Journal of Critical Reviews

ISSN- 2394-5125 Vol 6, Issue 5, 2019

Review Article

# CADMIUM NANOPARTICLES AND ITS TOXICITY

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*Received: 12 May 2019 Revised and Accepted: 13 Aug 2019*

**ABSTRACT**

Nanotechnology is the next-generation science revolutionized the world by providing many unpredicted outcomes. Though apparent beneficial, nanomaterials may associate with severe unknown health issues. People are exposed to nanoparticles during production, storage, shipping, utilization, and waste treatment process without adequate protection. Cadmium Sulfide Nanoparticles (*Cd. nps*) are used frequently to produce hybrid solar cells, semiconductors, Ni-Cd batteries, preparing metal alloys and coatings, fluorescence imaging and biosensing, light-emitting diode and plastic stabilizers. Toxicity of *Cd. nps* has raised a significant apprehension both, occupationally and environmentally yet no compiled data is available to signify its possible toxicity. Consequently, the present review meticulously evaluated the available literature and summaries the detrimental effect of cadmium sulfide nanoparticles. This attempt will specify existing knowledge of the toxic effects of cadmium-based nanoparticles and will aware personnel to minimize direct or indirect exposure.

**Keywords**: Cadmium sulfide, Nanotoxicology, Occupational exposure, Solar cell


DOI: http://dx.doi.org/10.22159/jcr.2019v6i5.34073

## INTRODUCTION

Nanotechnology is an emerging area of science and technology, providing high-performance materials, intelligent systems and novel product development methods. Research and development have been dramatically increasing worldwide for industrial production of nanomaterials [1]. It is estimated that by the year 2015, nanoproducts contributed approximately 1 trillion USD to the global economy [2]. Due to nanometer size ($10^{-9}$ meters) nanoparticles are representative of size-dependent novel physicochemical properties and stability [3].

### Uses of nanoparticles

Nanoparticle-based consumer products are already available for over-the-counter purchase; people do not even know what product they are using contain nanoparticles *e. g.* scratch-resistant car bumper, automotive catalytic converters, dirt repellant and odor-resistant textile, 'Smart' textile bearing electronics (wearable computers), radiation-resistant sunscreen, lightweight cell phone screens, longer shelf-life glass, cosmetic items, stronger synthetic bones, various durable sports balls, energy and electronics (low-cost electrodes for fuel cells that produces twelve times more catalytic activity than pure metal, conductive lines needed in circuit boards, Nanoparticle-Organic Memory Field-Effect Transistor (NOMFET) that function in a way similar to synapses in the nervous system, military weapons (biosensors to detect biological agents, clothes for thermal disguise and communication method), nanofibrils (lignin-cellulose, twofold stronger than steel) [4-8]. Nano foods (carrying vitamins, minerals, β-carotene and phytochemicals) [9], nano-filter paper to remove cholesterol or nicotine [10]. Eco-friendly nanoparticles to biodegrade oil into compounds, volatile air organic pollutants, clean up carbon tetrachloride and arsenic pollution in groundwater [11, 12]. Nanotechnology is also being applied in imaging biomarkers for disease detection and molecular diagnosis (streptavidin-coated fluorescent polystyrene in human epidermal carcinoma [13], ultrasensitive assay in serum Prostate-Specific Antigen (PSA) detection) [14], in MRI, CT, fluorescence imaging and ultrasound techniques [15-17]. Role of nanoparticles is very imperative in drug targeted specificity, absorption, solubility and constancy, especially for carboplatin, cisplatin, doxorubicin, 5-fluorouracil, octreotide, oxaliplatin, vincristine, and paclitaxel like antineoplastic agents for providing more competent cell-specific cytotoxicity [18-21]. Nanoparticles mediated vascular thrombosis in the carotid artery with platelets aggregation, decrease in bronchi and kidney cell adhesion was observed in rats [22-25]. Nanoparticles of cadmium in the form of cadmium sulfide, cadmium oxide cadmium telluride, cadmium selenide, *etc*. are also frequently used owing to unique properties. Though apparent industrially useful, cadmium is classified as a toxic, nonessential transition metal and human carcinogen by the *National Toxicology Program* [26]. Sub-chronic cadmium dose treatment caused toxic effects on biochemical and neurobehavioral parameters [27], caused alteration in glucose metabolism [28] also damaged liver [29] and kidney [30]. This review is mainly emphasizing on cadmium sulfide nanoparticles, its synthesis, and associated toxicity.

### Cadmium sulfide nanoparticles

Cadmium Sulfide Nanoparticles (*CdS. nps*) confirm distinctive physical, chemical and structural properties of their bulk-sized material. Owing to the unique melting point, crystal configuration, bandgap energy, optoelectronic absorption spectra, high stability, availability and ease of preparation and handling *CdS. nps* are used in routine life. In addition to surface/volume ratio, the atomic distribution over nanoparticle shell plays a crucial role in semi-conductivity [31]. *CdS. nps* are used as the pigment in paints and in engineered plastic industries due to their good thermal constancy as well as dirt repellent capability [32, 33]. *CdS. nps* have large band-gap-energy of 2.42 eV at room temperature that enables *nps* useful for optoelectronics *viz*. photocells, LED [34]; photonics *viz*. sensors, photo detectors, optical filters, and all-optical switches [35]; photovoltaics and photo catalysis e. g. lasers [36], field-effect transistors and address decoders [37]. Owing to both photochemical as well as catalytic properties *CdS. nps* can be used as the air-water purifier and for $H_2$ production [38]. Because of its high fluorescence and optical properties *CdS. nps* are used in diagnosis and treatment of different cancer types by accumulating nanoparticles inside malignant cells further visualized and irradiated with ultraviolet radiation for less harmful localized chemotherapy and/or radiotherapy (photodynamic cancer therapy) [39]. CdS nanoparticles can also be used in visualization as well as in drug delivery to the soft tissues *i.e.* retina and cornea [40, 41].

### Search criteria

A literature search was conducted in PubMed, Google Scholar and Scopus databases for articles published from May 1995 to January 2017 on synthesis and/or exposure to cadmium nanomaterials. Combinational keywords *i.e.* cadmium nanoparticles synthesis OR cadmium sulfide OR cadmium sulfide nanoparticles synthesis OR

cadmium sulfide nanoparticles toxicity OR cadmium sulfide nanoparticles neurotoxicity OR cadmium sulfide nanoparticles carcinogenicity OR mechanism of nanotoxicity were used as search criteria.

**Synthesis of CdS nanoparticles**

*CdS. nps* have been industrially manufactured due to applications in different fields**.** Different techniques have been implemented in constructing nano-form of CdS films or powder, for instance chemical precipitation [42], Chemical Vapor Deposition (CVD) [43], electron beam vacuum evaporation [44], laser ablation [45], spin-coating [34], RF-magnetron sputtering [46], physical evaporation [47], template synthesis [48], thermal evaporation [49], hydrothermal synthesis [50], Chemical Bath Deposition (CBD) [51], Physical Vapor Deposition (PVD) [52], pulsed laser deposition [53], solvothermal [54], simulating biomineralization [33], biosynthesis using bacteria, fungi, yeast and plants *etc.* [39] and electro-deposition [55]. Chemical precipitation technique is frequently used as it requires ambient environmental conditions, simple lab equipment, less time consuming and reliable results whereas as compare to rest of methods which require extreme environmental conditions, sophisticated equipment and are time-consuming too. The stability and size of *CdS. nps* is controlled by limiting the reaction area by using capping agents like EDTA, long-chain alkyl xanthates, mercaptoacetic acid, phosphates, phosphine oxides, thioglycerol, thiols and thiourea [56], glass, polymer, silica, vesicles, reverse micelles, zeolites, LB films, stabilizers and solvents (affect kinetics and synthesis reactions equilibria, and spectroscopic properties of solutes) [57].

Chicken egg-shell membrane as the host matrix was used for the synthesis of *CdS. nps* by diffusion of aqueous cadmium acetate and thiourea solutions [58]. $CdSO_4{\cdot}7H_2O$ and $Na_2S{\cdot}9H_2O$ used as precursors to synthesize *CdS. nps*. EDTA is used as the capping agent for controlling *nps* size [59, 60]. *CdS. nps* was prepared by adding aqueous $CdCl_2$, KOH, $NH_4NO_3$, $CS(NH_2)_2$ and stirring at pH10, temperature 80 °C for 30 min followed by centrifugation at 6000 rpm for 1 h [61]. *CdS. nps* were synthesized by chemical precipitation technique by deionized aqueous $CdCl_2$ and thiourea solution with continuous stirring at 100 °C for 15 h. Ammonia was added as the capping agent. The same method was also developed to synthesize triethylamine capped *CdS. nps* [62]. $CdCl_2$, sodium hydroxide (NaOH) and Hydrogen Sulfide ($H_2S$) mediated *CdS. nps* have been prepared. Aqueous NaOH and $H_2S$ gas were gradually added to methanol with continuous stirring for 4 h followed by adding $CdCl_2$ solution. Particles were separated at 10,00,000 ×g, washed thrice with methanol, dried and resuspended in Mili-Q water subsequently 4 times sonication for 30 min [63].

**Nanotoxicity**

Nanotoxicity refers to the metabolic as well as physiological interruptions in living organisms caused by engineered nanoparticles. Though the human is exposed to nanoscaled airborne particles since their evolutionary stages, the exposure has augmented considerably over the last century due to increased anthropogenic activities. It is estimated that only 2 g of nanoparticles (100 nm diameter) is sufficient for equal distribution to every human (0.3 million particles/person) [64]. Nanotoxicity has been studied in different biological systems, both in cell line systems and different organisms, which include aquatic species such as zebrafish [65], catfish [66] and rodents [67]. Wistar rats introduced with $TiO_2$ nanoparticles intraperitoneally thrice a week for 20 d, showed accumulation in brain, lung, and liver with high AST/ALT ratio, the abnormal neurobehavioral performance was observed in rats with significant liver histopathological observations [68]. Oral-single dose administration of $Al_2O_3$, ZnO and $TiO_2$ nanoparticles at 500 mg/kg translocated and accumulated at the Central Nervous System (CNS) to cause axillary toxicity, disrupting normal neurotransmitters metabolism and leading to brain damage ultimately [69]. Nanoparticles were dose-dependently found to degenerate the blood-brain barrier, inhibit cell survival in rat astrocytes and promote cerebral edema with tissue necrosis [70]. In addition, $MnO_2$ nanoparticles caused astrocyte activation, dopaminergic signaling deregulation resulting in cognition disabilities of rats [71]. Nanoparticles dermis exposure is mediated using wound dressings or cosmetic products containing nanoparticles for e. g. silver nanoparticle coated wound dressing is used for treatment in burn patients while silver nanoparticle-containing ointment is used for microbial infection which enters directly the dermis. In addition, $TiO_2$ nanoparticle in anti-tanning lotion exposes the deeper parts of hair follicles [72] and also caused neurotoxicity [73]. Nano-silver toxicity was reported in a burning patient who had received the silver-coated dressing for treatment [6, 74].

**Toxicity of cadmium nanoparticles**

Cadmium (Cd) has established a significant apprehension both occupationally and environmentally. In the biological system, it represents xenobiotic property by transporting from olfactory system to the centre peripheral neurons and biomagnified in liver, kidneys, spleen as well as in cerebrum which further increase the blood-brain-barrier permeability [75] (fig. 1). Cd exposure relentlessly disturbs the nervous system [76, 77], with symptoms including peripheral neuropathy, reduced vasomotor functioning, Parkinson like symptoms, decreased concentration, balancing and learning ability decreased [75, 78, 79]. QDs (size range from 2-20 nm) of Cd was extracellularly biosynthesized by *Escherichia coli* and the toxicity between biosynthesized and microwave prepared QDs was compared using HFF, PC-3, and MCF-7 cell lines as well as MTT assay. Toxicity was varying about 10 % in HFF, 30 % in MCF-7 cell lines. In comparison to microwave synthesis QDs, the toxicity of biosynthesized QDs to the PC-3 cell lines was about 35 % reduced [80]. Occupational exposure of Cd resulted in severe malignancy of stomach, liver, pancreas, lung, kidney, urinary bladder, prostate gland and hematopoietic system [81-83]. Capping with maltodextrin revealed a decrease in the toxicity of *nps*. Dose-dependent induction of apoptosis and necrosis *via* ROS production was observed by CdS-maltodextrin nanoparticles in MDA-MD-231 cells. Exposure of *CdS. nps* to chick embryos coated with maltodextrin resulted in a dose-depend increase in developmental anomalies though it was lesser than intact *CdS*. *nps* exposure. Low *CdS*. *nps* dose exposure found to be nontoxic and prescribed for bioimaging applications [84]. In addition, developmental abnormalities during embryogenesis were also observed by cadmium as well as silver nanoparticles exposure [85, 86]. Medium concentration of both micro-sized as well as nano-sized Cd particles, brought about a noteworthy diminution of cellular GSH content. N-acetylcysteine treatment partially protected the cells from *CdS. qds* though were exposed to micro-sized particles. The toxicity of *CdS. qds* may due to the release of cadmium which intracellularly produced Reactive Oxidative Damage (ROS) and depleted GSH contents to generate cytotoxicity [87]. A concentration-dependent decrease was observed in hatching in mercaptopropionic acid-coated *CdSe.* q*ds* in zebrafish with degenerated morphology [88]. Embryonic toxicity of *Cd. qds* was also observed [89]. Toxicity of Cd nanoparticles was evaluated during the detoxification process [90]. *In vivo* bioimaging following *CdS. nps* intraperitoneal treatment at 1.50 mg/kg depicted a fluorescence signal which was distributed RGY colors, indicative the presence of quantum dots. MTT assay of *CdS. qds* revealed more toxicity than its micro-sized particles even at less than 40 lg/ml concentration. Though micro-*CdS* particles did not activate ROS production, *CdS. qds* significantly augmented the ROS. Meng *et al.* [91] reported the induction of liver injury by cadmium sulfide nanoparticles and also explored the possible hepatotoxicity mechanism induced by *CdS. nps.* It was observed that *CdS. nps* administration brought about significant infiltration in hepatic inflammatory cells with changed hepatic ultrastructure. The activities of Total Antioxidant Capacity (TAOC) and GSH were decreased with concomitant increase in lipid peroxide (MDA) content. Additionally, decreased Sirt1 and FoxO1 mRNA expression in liver tissue was observed. Cytotoxic study of water-dispersible quantum dots of *CdS. qds* was observed by Mirnajafizadeh *et al.* [92] using HCT-116 cells. Decreased cell viability with cell stability at different concentrations of quantum dots confirmed the cytotoxicity of *CdS. qds*. In a study conducted by Rana *et al.* [93] renal toxicity of *CdS. nps* were estimated. Alternate day exposure for 45 d with *CdS. nps* at 10 mg/kg b. wt. revealed marked increase in Cadmium Metallothionein (Cd-MT), lipid peroxidation and $H_2O_2$ generation in kidney as compared to bulk-sized cadmium. Urine creatinine

concentration was also increased following *CdS. nps* exposure. Damaged renal proximal tubules with loss of alkaline phosphatase, altered mitochondrial, nuclear and endoplasmic reticulum was seen following *CdS. nps* exposure [93].

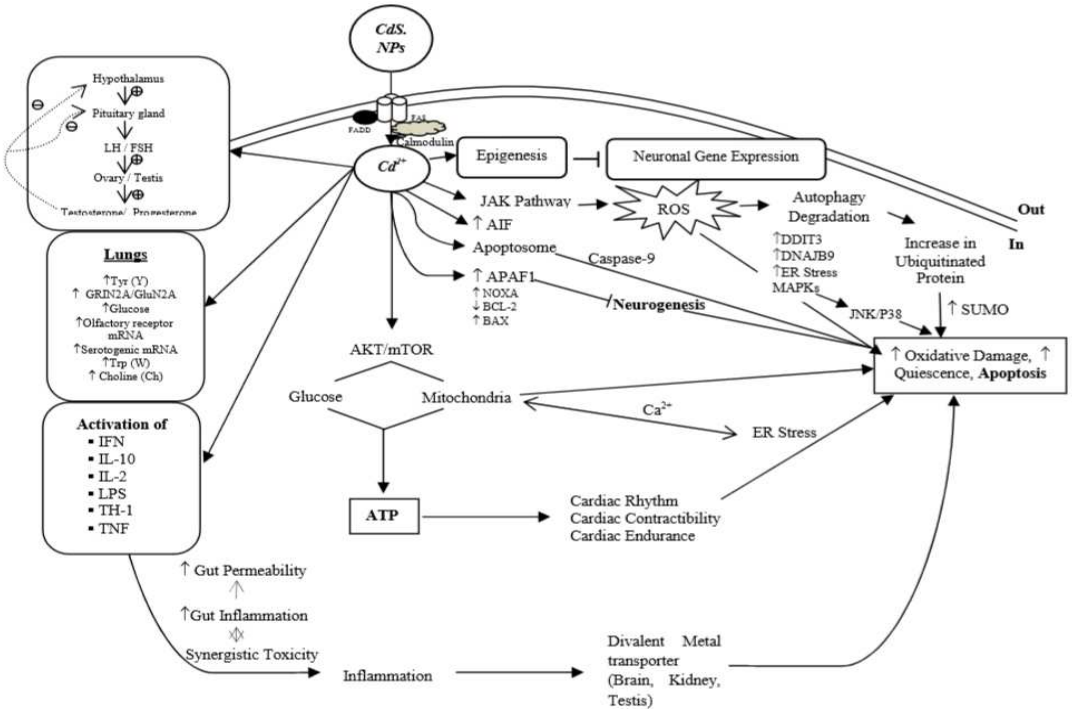


**Fig. 1: Neuronal toxicity of cadmium [75, 109]**

**Possible mechanism of nano-cytotoxicity**

***ROS generation and cytotoxicity***

Oxidative stress induces the ROS over-generation by disturbing standard redox-regulated physiological and developmental functions resulting in the generation of modified AOPP [94, 95] (fig. 2). These modified proteins change the gene expression through activation of redox-sensitive transcription factors [96, 97], initiate DNA-strand breaks, modify nucleic acids [98], enhances lipid peroxidation [99-101] and intonation of inflammatory responses [75, 102], leading to cytotoxic and genotoxic effects [103-105]. Age-related degenerative changes including arthritis, amyotrophic lateral sclerosis, cardiovascular disease, inflammation, Alzheimer's disease, Parkinson's disease, diabetes, and cancer are also associated with increased ROS production [99, 106-108]. Cadmium-induced apoptosis in testicular cells resulting in male infertility through ROS-mitochondrial oxidative stress and JNK signaling pathway is also reported recently [109].

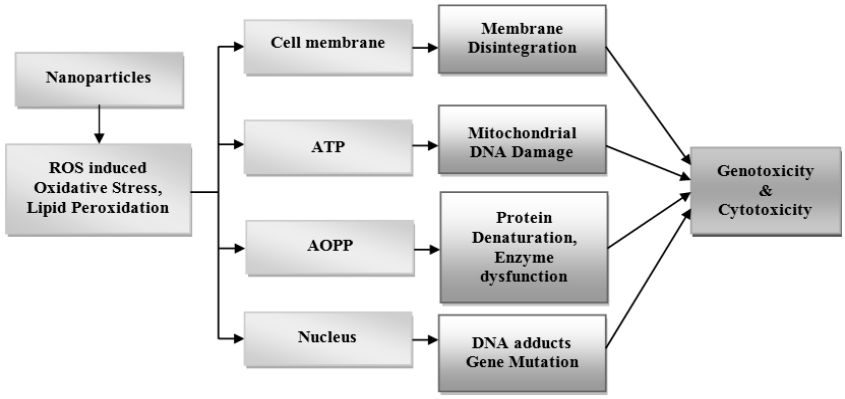


**Fig. 2: Nanotoxicity induced oxidative stress [104]**

***Generation of ROS***

Due to small size, increased surface area, and resultant high reactivity of nanoparticles, ROS level is augmented causing adverse genotoxic and cytotoxic outcomes [110]. ROS mediated oxidative stress is a predominant mechanism leading to nanotoxicity effects which include cytotoxicity, deregulation of signaling pathways, DNA damage, and malignancy [111]. Nanoparticles and their physicochemical nature directly affect the ROS generation [65]. Nanotoxicity has been reviewed in human erythrocytes and skin fibroblasts [112]. Nanoparticle-induced oxidative stress and resultant cytotoxicity were reported dose-dependently *via* stimulation of ROS and lipid peroxidation in the cell membrane. Mouse Embryonic Fibroblasts (BALB-3T$_3$) showed dose-dependent

cytotoxicity by releasing LDH, and by inducing ROS mediated oxidative stress as well as lipid peroxidation [113]. Further confirmation of ROS induced cytotoxicity was reported by Fan and Lu [114] providing that *NPS* mediated the oxidative injury by releasing inflammation mediators, resulting in phagocytic murine RAW 264.7 cell death as well as Transformed Human Bronchial Epithelial (BEAS-2B) cells. ROS and C-Jun-terminal-kinase-dependent apoptosis were observed in NIH3$T_3$ cells, mediated *Ag. nps* induced mitochondrial pathway [115]. *Ag. nps* induced mutation, ROS formation and oxidative stress in mouse lymphoma cells were observed by Mei *et al.* [116]. Keratinocytes and bronchial epithelial cells exposed to SWCNTs produced ROS, lipid peroxidation, genotoxicity, and mitochondrial dysfunction *Ag. nps* induced oxidative stress and apoptosis in cultured animal cells [117]. Nanoparticle exposure can develop a wide range of DNA damage including chromosomal fragmentation, DNA strand lesion and induction of gene mutations [118-120]. *Au. nps* have been reported the formation of 8OHdG in embryonic lung fibroblasts by damaging DNA and down-regulation of mitotic checkpoint genes *i.e. APC/C, BUB3*, *cyclin B1, cyclin B2, CDC20 MAD1* and *MAD2* [121, 122]. This oxidative stress-induced DNA damage either cause cell cycle arrest resulting in apoptosis or begin DNA repair mechanism. Gene expression responsible for DNA damage was found to be altered following nanoparticle exposure. The PTEN and p53 genes play a pivotal role to activate the response to DNA damage, thereby preventing mutagenesis and carcinogenesis [123]. *CdS. qds* considerably increased the gene levels and upregulated Bax, Bazooka, aPKC, PAR-6, pAKT, Puma, and Noxa (p53 and PTEN associated genes) gene expression in human breast carcinoma cells [25, 124].

### *Inflammatory Nanotoxicity*

Inflammatory response induces the clearance of pathogenic molecule or accumulating a specific immunogenic response in bronchial and alveolar epithelium, monocyte and macrophage cells as well as keratinocytes using carbon nanomaterial [125, 126]. The mechanism of action of *nps* mediated inflammation perhaps owing to recognition by Toll-like receptors, interleukins and chemokines [127]. The precise mechanism of inflammatory action for nanotoxicity has not been so far revealed [25]. Nanomaterial induced immunogenic response may be due to their adjuvant like behavior and thus triggering antigenic response [128], which depends on physicochemical properties of nanomaterials *i.e.* size, surface charge and surface area [129]. The inflammatory response may result in toxicity also induces apoptosis/necrosis by incorporating ROS substances as well as complement proteins and glycoproteins (synthesized mainly by hepatocyte, macrophages, monocytes and genitourinary and gastrointestinal tracts epithelia) [130]. ROS-oxidative stress also reports pro-inflammatory mediators' release through various signal transduction pathway like MAPK, NF-κB and PI3K pathways. During inflammation-oxidative stress, down-regulator of NF-κB, IκB (which deactivate NF-κB) degrades and releases NF-κB, which further translocate to the nucleus and upregulate the target gene expression [131]. The nuclear translocation, activation of NF-κB following inflammatory mediators gene upregulation is supported by the production of $OH^{\cdot}$, $HOCl^{\cdot}$, and $^1O_2{}^{\bullet}$ lung injury and pulmonary fibrosis following nanoparticle exposure lead to ROS-generated NF-κB activation and production of the pro-inflammatory mediator (IL-2, IL-6, IL-8, and TNF-α) [132]. In this regard, a number of *nps* including Cd, Fe, Si, and Zn have been proved toxic by producing and secreting NF-κB mediated inflammatory cytokines [133]. Moreover, the production of MCP-1 and TNF-α with the promotion of inflammatory responses in mice was observed, following exposure to both single-walled and multi-walled carbon nanotubes [134]. MAPK, member of serine/threonine protein kinases for *e. g.* JNK, ERK, and p38 MAPK is found to regulate a variety of cellular responses *viz.* cell survival, mitosis, differentiation, cell proliferation, and cell death. *Ti. nps* caused toxicity in human bronchial epithelial cells by the release of p38 MAPK (regulate responses to cellular stresses) mediated IL-8 and/or ERK pathway (associated with cell proliferation and differentiation) [135]. Though preliminary studies are conducted to reveal nanoparticle-induced cytotoxicity and resulting autophagy pathways yet proper conclusion has not been drawn, therefore more studies are required to fully explore and recognize the cell signaling pathway [25].

### Perspectives

Unrestrained commercialization of CdS nanomaterial for developing novel technologies skyrocketed so speedily, lagging behind all the safety and toxicity concerns. Nano-scale size and high surface area enhance the tissue penetration, surface reactivity and potential toxicity of nanoparticle. To avoid or minimize the side-effect it is necessary to become aware of its toxicity issues. Nanomaterial induced cellular toxicity has been critically elucidated by a detailed biochemical pathway involving free radicals and oxidative stress. Knowledge about exposure side-effects will facilitate us to avoid or search for novel nontoxic or natural alternatives of CdS nanomaterial. Antioxidants play a pivotal role in managing and/or diminishing the damage caused by ROS. In this scenario, it is also important to observe the role of enzyme defense mechanism (SODs, peroxidases, glutathione peroxidase/reductase and catalases) against these toxic substances following exposure. The better understanding of nanotoxicology of cadmium sulfide may aware people to avoid or minimize its utilization, and may also direct to search alternative strategies to prevent nanomaterial-induced toxicity.

### ABBREVIATION

8OHdG: 8-hydroxydoxyguanosine: $Al_2O_3$: Aluminum oxide; AOPP; Advance oxidative protein products; AST/ALT: Aspartate aminotransferase/Alanine aminotransferase; Cd. nps: Cadmium nanoparticles; $CdCl_2$: Cadmium chloride; Cd-MT: Cadmium metallothionein; CdS: Cadmium sulfide; CdSe: Cadmium-selenium; $CdSO_4{\cdot}7H_2O$: Cadmium sulfate; CNS: Central nervous system; EDTA: Ethylene diamine tetra acetic acid; FETs: Field-effect transistors; HFF: Human Foreskin Fibroblast; IκB: Inhibitor of Nuclear Factor-κB; LDH: Lactate dehydrogenase; LED: Light emitting diode; MAPK: Mitogen-Activated Protein Kinase; MCP-1: Monocyte Chemoattractant Protein-1; MRI: Magnetic resonance imaging; MTT: 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide; $Na_2S{\cdot}9H_2O$: Sodium sulphide; NF-κB: Nuclear factor-κB; NOMFET: Nanoparticle-organic memory field-effect transistor; nps: Nanoparticles; PCD: Programme cell death; PEG: Polyethylene glycol; PI3K: phosphoinositide 3-kinase; PSA: Prostate-specific antigen; ROS: Reactive oxidative species; SWCNTs: Single walled carbon nanotubes; $TiO_2$: Titanium dioxide; TAOC: Total antioxidant capacity; XRD: X-ray diffraction; ZnO: Zinc oxide.

### ACKNOWLEDGMENT

Author is thankful to Director, ICMR-NIOH for providing necessary facilities.

### AUTHORS CONTRIBUTIONS

All the author have contributed equally

### CONFLICT OF INTERESTS

The author declares that there is no conflict of interest

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